Australian Government
Department of Health
Australian Industrial Chemicals Introduction Scheme

Glycidyl acrylate and glycidyl methacrylate

Evaluation statement

30 June 2022

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AICIS Evaluation Statement

Subject of the evaluation

Glycidyl acrylate and glycidyl methacrylate

Chemicals in this evaluation

Name	CAS Registry Number
2-Propenoic acid, 2-oxiranylmethyl ester	106-90-1
2-Propenoic acid, 2-methyl, 2-oxiranylmethyl ester	106-91-2

Reason for the evaluation

The Evaluation Selection Analysis indicated a potential risk to human health.

Parameters of evaluation

Chemicals in this evaluation are a group of glycidyl esters of acrylic and methacrylic acid that are listed on the Australian Inventory of Industrial Chemicals (the Inventory). This evaluation is a human health risk assessment for all identified industrial uses of these chemicals. This group of chemicals have similar use patterns and are expected to have similar toxicological properties, which are mainly expected to result from either direct reactions of the epoxide group or the metabolite glycidol.

Summary of evaluation

Summary of introduction, use and end use

There is currently no specific information about the introduction, use and end use of these chemicals in Australia.

Based on international use information, these chemicals are expected to be used as starting monomers. The reactive polymers and pre-polymers manufactured from these chemicals are used in number of industrial products including:

- powder and metal coatings
- paints and coating products
- adhesive products
- two-part resins
- printing inks
- rubber and plastic products
- food contact materials.

Human health

Summary of health hazards

Limited data are available for glycidyl acrylate (GA). Given their close structural similarities, data for glycidyl methacrylate (GMA) and the common metabolite glycidol, are used to draw conclusions on health hazards.

Based on the available information, these chemicals can cause several acute, local and chronic health effects, including acute toxicity, severe skin and eye damage, skin sensitisation, damage to the respiratory system through inhalation, mutagenicity, carcinogenicity and adverse effects on fertility.

Chemicals in this group are expected to be readily absorbed following oral, dermal and inhalation exposure. Available in vitro and in vivo studies for GMA indicate carboxylesterase-mediated hydrolysis of GMA to glycidol and methacrylic acid. Although no toxicokinetic data is available on GA, based on its chemical structure, its toxicokinetic profile is expected to be similar to GMA, and it will metabolise to glycidol and acrylic acid.

Based on available data, these chemicals are expected to have moderate to high acute oral toxicity and high dermal acute toxicity. The available inhalation studies for GMA indicate no mortality up to the saturated vapour pressure. Although GA is classified as toxic if inhaled, there are insufficient data to review or amend this classification.

Based on the available data, these chemicals are corrosive to the skin, considered to induce serious eye damage and cause irritation to the respiratory tract. Necrotic effects to skin were observed in studies with GMA in rabbits. Corrosive effects were not observed in one study in which rabbits were exposed to GMA for one hour. The data available for GMA indicated corneal damage following direct application and exposure to vapours. In some acute inhalation studies, GMA caused laboured breathing in rats and treatment related irritation in lungs, thorax and respiratory tract in rats, rabbits, guinea pigs and dogs. No data are available for GA. There are insufficient data to review or amend the current sub-category of the corrosivity classification for GA.

Based on available data these chemicals are considered to be skin sensitisers which is consistent with other acrylates and methacrylates. Positive results were reported in an in vivo skin sensitisation study (Buehler) conducted in guinea pigs with GMA.

Based on the available data, these chemicals cause tissue damage at the site of contact following repeated exposure. This finding is consistent with the hydrolysis of these chemicals at the site of contact. Treatment related effects in studies with GMA included tissue damages in the first exposure sites to the chemical, such as the forestomach (by oral administration) and upper respiratory tract (by inhalation), caused by the irritation properties of the chemical. The NOAELs were 10 mg/kg bw/day for local effects in rats by the oral route, 12 mg/m^3 in rat by the inhalation route, and 2.91 mg/m^3 in rabbits by the inhalation route. Although these effects are consistent with the corrosive nature of the chemical, effects on the respiratory tract by inhalation occurred at doses significantly lower than those observed following acute exposure. No repeated dose toxicity data are available for GA, but it is expected to cause similar damage to the respiratory tract based on its corrosive properties.

Based on the available data for GMA and the metabolite glycidol, these chemicals are considered to have genotoxic and carcinogenic potential. In available in vitro genotoxicity studies on GMA, including the bacterial reverse mutation test, chromosome aberration test, and cell gene mutation test, the results were consistently positive. In all available studies in

human primary cells, glycidyl methacrylate induced DNA damage, including double strand breaks and unscheduled DNA synthesis. Although mixed results were reported in vivo, GMA was positive in an in vivo mouse micronucleus assay. In a study in F344 rats, repeated exposure to GMA resulted in DNA damage in bone marrow, liver and kidney tissue, increased micronucleus formation in erythrocytes from peripheral blood and increased frequencies of mutant red blood cells.

Limited data are available for GA. GA was positive in an Ames test for all strains of *Salmonella typhimurium* TA97, TA100 and TA1535.

In a 2 year inhalation study in mice with GMA, haemangioma and haemangiosarcoma in the nasal cavity were observed in males and females. In female mice, there was a significant positive trend and increase in the incidence of bronchioalveolar carcinoma. In a 2 year inhalation study in rats with GMA, squamous cell carcinoma of the nasal cavity was observed in males and females. Tumours were also observed at other sites including the peritoneum, skin and subcutis and mammary gland. The metabolite glycidol is classified for Carcinogenicity – Category 1B, and Germ cell mutagenicity – Category 1B). The tumour site profile of GMA is similar to that reported in carcinogenicity bioassays with glycidol.

Based on the available data, these chemicals are expected to cause specific adverse effects on fertility following exposure. Similar to the metabolite glycidol, male reproductive function appears to be the sensitive adverse effect. A combined repeated dose and reproductive/ developmental toxicity screening test was conducted on rats using GMA. The fertility index decreased significantly at the high dose. Reduced sperm motility was also reported. The study authors considered NOAELs for reproductive toxicity and developmental toxicity to be 30 mg/kg bw/day and 100 mg/kg bw/day, respectively. Decreased sperm counts and increased abnormal sperm were observed in 2 studies in mice following exposure by intraperitoneal injection. An NOAEL of 5 mg/kg bw/day was reported for sperm toxicity. Based on the available developmental studies for GMA by oral and inhalation routes, these chemicals are not expected to cause developmental toxicity. There was no evidence of teratogenicity even at the highest doses which showed maternal toxicity.

Health hazard classification

These chemicals satisfy the criteria for classification according to the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) (UNECE 2017) for hazard classes relevant for work health and safety as follows. This does not consider classification of physical hazards and environmental hazards.

The classifications with * should be considered to apply for GA only, and the ones with ^ should be considered to apply for GMA only.

Health Hazards	Hazard Category	Hazard Statement
Acute Toxicity – oral*	Acute Tox. 3	H301: Toxic if swallowed.
Acute Toxicity – oral^	Acute Tox. 4	H302: Harmful if swallowed.
Acute Toxicity – dermal	Acute Tox. 3	H311: Toxic in contact with skin
Skin Corrosion*	Skin Corr. 1B	H314: Causes severe skin burns and eye damage

Skin Corrosion^	Skin Corr. 1C	H314: Causes severe skin burns and eye damage
Skin Sensitisation	Skin Sens. 1	H317: May cause an allergic skin reaction
Serious eye damage	Eye Damage 1	H318: Causes serious eye damage
Acute Toxicity – inhalation*	Acute Tox. 3	H331: Toxic if inhaled
Specific Target Organ Toxicity (single exposure)	STOT Single Exp. 3	H335: May cause respiratory irritation
Germ Cell Mutagenicity	Muta. 2	H341: Suspected of causing genetic defects
Carcinogenicity	Carc. 1B	H350: May cause cancer
Reproductive and Developmental Toxicity	Repr. 1B	H360F: May damage fertility
Specific Target Organ Toxicity (repeated exposure)	STOT Rep Exp. 1	H372: Causes damage to respiratory tract through prolonged or repeated exposure through inhalation

Summary of health risk

Public

Based on the available use information, it is unlikely that the public will be exposed to these chemicals. Although the public could be exposed to products manufactured with these chemicals, these chemicals will be fully reacted with other components and bound to the matrix of the substrates. In migration studies from polymers manufactured from GMA used as food contact materials, GMA was below the limit of detection (EFSA 2011; EFSA 2012a; EFSA 2012b). Therefore, there are no identified risks to the public that require management.

Workers

During product formulation, dermal, ocular and inhalation exposure might occur, particularly where manual or open processes are used. These could include transfer and blending activities, quality control analysis, and cleaning and maintaining equipment. Worker exposure to these chemicals at lower concentrations could also occur while using formulated products containing these chemicals. The level and route of exposure will vary depending on the method of application and work practices employed.

Given the critical systemic and local effects, these chemicals could pose a risk to workers unless adequate control measures to minimise dermal, ocular and inhalation exposure are implemented (see **Proposed means for managing risk** section).

Once the chemical products are cured, these chemicals will be fully reacted with other components and bound to the matrix of the substrates. Therefore, these chemicals are not expected to be available for exposure to users of products.

Proposed means for managing risk

Workers

Recommendation to Safe Work Australia

It is recommended that Safe Work Australia (SWA) update the Hazardous Chemical Information System (HCIS) to include classifications relevant to work health and safety. Current notes should be retained.

Information relating to safe introduction and use

The information in this statement including recommended hazard classifications, should be used by a person conducting a business or undertaking (PCBU) at a workplace (such as an employer) to determine the appropriate controls under the relevant jurisdiction Work Health and Safety laws.

Control measures that could be implemented to manage the risk arising from exposure to these chemicals include, but are not limited to:

- using closed systems or isolating operations
- using local exhaust ventilation to prevent these chemicals from entering the breathing zone of any worker
- minimising manual processes and work tasks through automating processes
- adopting work procedures that minimise splashes and spills
- cleaning equipment and work areas regularly
- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with these chemicals.

Measures required to eliminate or manage risk arising from storing, handling and using these hazardous chemicals depend on the physical form and how these chemicals are used.

These control measures may need to be supplemented with:

- conducting health monitoring for any worker who is at significant risk of exposure to these chemicals, if valid techniques are available to monitor the effect on the worker's health.

Personal protective equipment should not solely be relied upon to control risk and should only be used when all other reasonably practicable control measures do not eliminate or sufficiently minimise risk.

Model codes of practice, available from the Safe Work Australia website, provide information on how to manage the risks of hazardous chemicals in the workplace, prepare an SDS and label containers of hazardous chemicals. Your Work Health and Safety regulator should be contacted for information on Work Health and Safety laws and relevant Codes of Practice in your jurisdiction.

Conclusions

The conclusions of this evaluation are based on the information described in this statement.

Considering the proposed means of managing the risks, the Executive Director is satisfied that the identified human health risks can be managed within existing risk management frameworks provided all requirements are met under environmental, workplace health and safety and poisons legislation as adopted by the relevant state or territory and the proposed means of managing the risks are implemented.

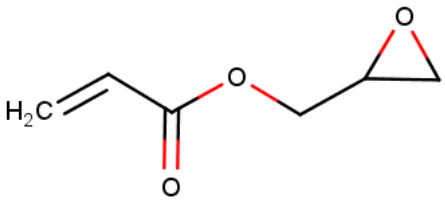
Note: Obligations to report additional information about hazards under *Section 100 of the Industrial Chemicals Act 2019 apply.*

Supporting Information

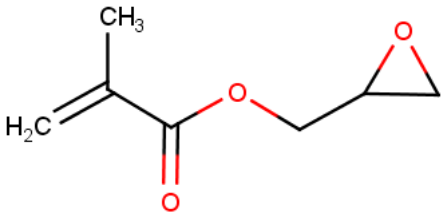
Grouping rationale

Chemicals in this group evaluation are glycidyl esters of acrylic (CAS No. 106-90-1; GA) and methacrylic acid (CAS No.106-91-2; GMA). These chemicals have similar uses and bioavailability. These chemicals metabolise to glycidol (CAS No. 556-52-5) which is expected to dominate their systemic toxicity. Glycidol has been previously assessed under our former scheme, the National Industrial Chemicals Notification and Assessment Scheme (NICNAS 2014a). The findings from that assessment will be used to support information on toxicological endpoints of GA and GMA.

Chemical identity

Chemical name	2-Propenoic acid, 2-oxiranylmethyl ester
CAS No.	106-90-1
Synonyms	glycidyl acrylate (GA) 2,3-epoxypropyl acrylate acrylic acid, 2,3-epoxypropyl ester
Structural formula	
Molecular formula	C6H8O3
Molecular weight (g/mol)	128.13
SMILES	O=C(OCC1OC1)C=C
Chemical description	Not specified

Chemical name	2-Propenoic acid, 2-methyl, 2-oxiranylmethyl ester
CAS No.	106-91-2
Synonyms	glycidyl methacrylate (GMA) 2,3-epoxypropyl methacrylate methacrylic acid, 2,3-epoxypropyl ester oxiranyl methyl methacrylate oxiranylmethyl 2-methyl-2-propenoate

Structural formula	
Molecular formula	C7H10O3
Molecular weight (g/mol)	142.15
SMILES	O=C(OCC1OC1)C(=C)C
Chemical description	-

Relevant physical and chemical properties

Chemical	Glycidyl acrylate (GA)	Glycidyl methacrylate (GMA)
Physical form	colourless to yellow liquid	colourless liquid
Freezing Point	-42 °C	-10 °C
Boiling point	65 °C	196.8 – 197.9 °C
Vapour pressure	4.0 × 10^2 Pa at 25 °C	4.2 × 10^2 Pa at 25 °C
Water solubility	55.3 g/L at 25 °C	~50 g/L at 25 °C
log K_{OW}	0.27 at 25 °C	0.96 at 25 °C

Introduction and use

Australia

No specific information is available on the introduction, use and end use of these chemicals in Australia.

International

The following international uses have been identified through EFSA Scientific opinions (EFSA); the European Union Registration, Evaluation and Authorisation of Chemicals (REACH); ECHA CLP report; ChemWatch; United States Environmental Protection Agency (US EPA); International Agency for Research on Cancer (IARC) monograph volume 125; and Organisation for Economic Co-operation and Development (OECD) SIDS Initial Assessment Report (2000).

These chemicals have reported site-limited use as a monomer. The reactive polymers and pre-polymers manufactured from GMA have reported use in the following industrial products:

- powder and metal coatings
- paints and coating products
- adhesive products
- two-part resins
- printing inks
- rubber and plastic products.
- food contact materials.

GMA is reported to have non-industrial site limited uses in the manufacture of polymers and pre-polymers used in medical applications such as:

- dental sealants and bone composite materials
- hydrogel lenses.

Existing Australian regulatory controls

AICIS

No specific controls are currently available for these chemicals.

Public

No specific controls are currently available for these chemicals.

Workers

These chemicals are listed in the Hazardous Chemical Information System (HCIS) (SWA) with the following hazard category and statements for human health.

Chemical	Hazard Category	Hazard Statement
Glycidyl acrylate (GA) (CAS No. 106-90-1)	Acute toxicity—category 3	H301 (Toxic if swallowed)
	Acute toxicity—category 3	H311 (Toxic in contact with skin)
	Acute toxicity—category 3	H331 (Toxic if inhaled)
	Skin corrosion—category 1B	H314 (Causes severe skin burns and eye damage)
	Skin sensitisation—category 1	H317 (May cause an allergic skin reaction)

Chemical	Hazard Category	Hazard Statement
Glycidyl methacrylate (GMA) (CAS No. 106-91-2)	Skin sensitisation—category 1	H317 (May cause an allergic skin reaction)
	Carcinogenicity—category 1B	H350 (May cause cancer)
	Germ cell mutagenicity—category 2	H341 (Suspected of causing genetic defects)
	Reproductive toxicity—category 1B	H360F (May damage fertility)
	Specific target organ toxicity (single exposure) —category 3	H335 (May cause respiratory irritation)
	Specific target organ toxicity (repeated exposure)—category 1	H372 (Causes damage to respiratory tract through prolonged or repeated exposure by inhalation)
	Skin corrosion—category 1C	H314 (Causes severe skin burns and eye damage)
	Acute toxicity (ingestion)—category 4	H302 (Harmful if swallowed)
	Acute toxicity (dermal)—category 3	H311 (Toxic in contact with skin)

These classifications are subject to the following notes:

D (Certain substances which are susceptible to spontaneous polymerisation or decomposition are generally placed on the market in a stabilised form. It is in this form that they are listed in this spreadsheet. However, such substances are sometimes placed on the market in a non-stabilised form. In this case, the supplier should state on the label the name of the substance followed by the words 'non-stabilised'.)
8 (The tables in schedule 6 of the WHS regulations replace some tables in the GHS, this may affect the cut off concentrations for this chemical.) No exposure standards are available for these chemicals in Australia (SWA).

International regulatory status

Exposure standards

The following exposure standards are identified for GA: (Galleria Chemica):

- Protective action criteria (PAC) (formerly known as Temporary Emergency Exposure Limits (TEELS)) in the United States (US) of PAC-1 = 0.081 ppm, PAC-2 = 0.089 ppm, and PAC-3 = 5.4 ppm

The following exposure standards are identified for GMA:

- China Occupational Exposure Limits for Hazardous Agents in the Workplace of 5 mg/m^3(maximum allowable concentration)
- Japan Occupational Exposure Limits (TWA) of 0.01 ppm (0.06 mg/m^3)
- US Toxicology Excellence for Risk Assessment (TERA) Workplace Environmental Exposure Levels (WEEL) of 0.5 ppm over 8 hours.

Europe

The chemical GMA is listed in the Commission regulation (EU) No. 10/2011 on plastic materials and articles intended to come into contact with food with a specific migration limit (SML) of 0.02 mg/kg food (EC, 2011).

The chemical GMA is listed in Regulation (European Commission (EC)) 1223/2009 on cosmetic products, Annex II – List of substances prohibited in cosmetic products.

United States of America

The chemical GMA is listed in the U.S. Food and Drug Administration's Code of Federal Regulations in the section for indirect food additives as a substance permitted for use in components of adhesives and uncoated or coated surface of paper and paperboard, subject to the provisions of such regulation (US FDA).

Health hazard information

Toxicokinetics

Based on the molecular weights and K_{OW} values of these chemicals are expected to be absorbed following oral, dermal and inhalation exposure. This is supported by observations of effects following all routes of exposure. The epoxide group of these chemicals is highly reactive, leading to local effects at the point of contact.

The in vitro and in vivo studies for GMA indicate that, after systemic absorption of these chemicals, carboxylesterase-mediated hydrolysis of GMA to glycidol occurs. Although the metabolic transformation may be slower in humans than in rodents, the primary metabolite of GMA in humans, rats and rabbits was glycidol.

In an in vivo study on rabbits, 200 mg/kg bw of GMA was administered by intravenous injection. Over 95 % of the test substance was eliminated from the blood within 10 minutes, indicating rapidly metabolism of the test substance likely by carboxylesterase to glycidol and methacrylic acid. Following a subcutaneous injection at 800 mg/kg bw, the toxicokinetics appeared to fit a first order absorption one compartment open model. The levels of the test substance in blood were increased 10-fold in rabbits co-administered a carboxylesterase inhibitor (tri-o-cresyl-phosphate). These chemicals metabolise to glycidol which is expected to dominate the toxicity of these group of chemicals (ECHA 2015a; OECD 2000; REACH).

An in vitro toxicokinetics study was conducted on human, rat and rabbit liver and respiratory tract epithelium cell fractions. Incubations of radiolabelled GMA with tissue preparations resulted in the formation of only one metabolite. The biotransformation was faster in rats and rabbits as compared to humans (completed within 30 minutes versus 2 hours), under all circumstances only one metabolite appeared which was tentatively identified as glycidol, based on retention time match with ^{14}C-glycidol (ECHA 2015a; OECD 2000; REACH).

No specific toxicokinetic data are available for GA. Based on information from other acrylic esters (NICNAS 2014b; NICNAS 2015), the metabolic pathway is expected to be similar to GMA with metabolism likely by carboxylesterase to glycidol and acrylic acid.

Acute toxicity

Oral

Based on available data, chemicals in this group are expected to have moderate to high acute oral toxicity. Although no guideline studies are available, the reported median lethal dose (LD50) values are consistent with the current hazard classifications.

For GA, LD50 values of 210 mg/kg bw and 150 mg/kg bw were reported in 2 studies in rats and a LD50 of 89 mg/kg bw was reported in rabbits (NLM). For GMA, LD50 values in the range 141–1050 mg/kg bw were reported in rats (ECHA 2015a; OECD 2000; REACH).

Dermal

Based on the limited data available, these chemicals are expected to have high acute dermal toxicity. The reported LD50 value for GMA is consistent with the current classification. While the available data for GA do not support the current classification, in the absence of more comprehensive information, there is insufficient evidence to warrant an amendment to this classification.

A dermal LD50 of 63 mg/kg bw was reported in rabbits with GA (NLM) and LD50 of 480 mg/kg bw for GMA (ECHA 2015; OECD 2000; REACH).

Inhalation

Although GA is classified as toxic if inhaled, there are insufficient data to review or amend this classification. A lethal concentration low (LCLo) of 125 ppm/4 hours or 655 mg/m^3 was reported in rats. No study details are available (NLM).

The available inhalation studies for GMA indicate no mortality up to the saturated vapour pressure. Higher concentrations, including aerosols, were not tested.

Based on an inhalation toxicity study (according to OCED Test Guideline (TG) 403) conducted in F344/N rats (n=5/sex/dose), no mortality was observed in rats treated with GMA for 4 hours at concentrations of 610, 1563 or 2394 mg/m^3. However, laboured respiration, eye irritation with corneal opacity, and decreases in body weight were observed at 1563 mg/m^3 and 2394 mg/m^3 (ECHA 2015a; OECD 2000; REACH).

In a non-guideline inhalation toxicity study conducted in rats, no mortality was observed following exposure to saturated vapour of GMA at 2754 mg/m^3 (at 20 °C) for 2 hours (ECHA 2015a; OECD 2000; REACH).

In a non-guideline acute inhalation study with GMA exposure at 1400 mg/m^3 for 6 hours, treatment related changes in lungs, thorax and respiration were observed in rats, rabbits, guinea pigs and dogs.

Corrosion/Irritation

Skin corrosion

These chemicals are both classified as corrosive, but have different subcategories applied. The available data for GMA are consistent with the current classification. There are insufficient data to review or amend the sub-category for GA.

In a Department of Transportation (DOT) standard test equivalent to OECD TG 404, moderate necrosis was observed in 2/6 NZW rabbits after a 4 hour exposure to GMA; corrosive effects were not observed following one hour exposure (ECHA 2015a; OECD 2000; REACH).

In a non-guideline in vivo skin irritation study, GMA (0.1 mL of 1% GMA in acetone) was applied to the skin of rabbits for 5 days. The treated areas were red, swollen and blistered after 2 days of application. Subdermal bleeding and ulcers were observed after 3 days and hard, thickened and cracked skin with pigmentation was observed after 5 days. The pathological changes included degeneration and necrosis of surface skin cells, disappearance of cellular boundaries with pink staining, bleeding in the corium cells and lymph cell infiltration with accompanying formation of abscesses (ECHA 2015a; OECD 2000; REACH).

In a skin irritation study in albino rabbits, a single topical application of 10 % aqueous GMA solution induced moderate to severe irritation with necrosis after one application for 4 hours and moderate burns after 2 applications (ECHA 2015a; OECD 2000; REACH).

Eye irritation/damage

As these chemicals are corrosive to skin, they are also considered to induce serious eye damage. Limited data available for GMA indicated corneal damage following direct application and exposure to vapours.

In an in vivo eye irritation study, GMA (undiluted) was applied to the eyes of rabbits. The chemical induced moderate to severe irritation and corneal damage after application. No effects were reversed within the 7 days of the study period (ECHA 2015a; OECD 2000; REACH).

Irreversible corneal opacity was observed in 2 inhalation studies in rats at doses from 610−2394 mg/m^3 and 931 mg/m^3, respectively (ECHA 2015a; REACH).

Respiratory irritation

The chemical GMA is classified as ‘Specific target organ toxicity (single exposure) – Category 3’ classification. The reported laboured breathing and changes in the respiratory tract in the acute inhalation studies together with the corrosive properties of the chemical are consistent with this classification (ECHA 2015b). No respiratory irritation data are available for GA, but it is expected to cause similar damage to the respiratory tract based on its corrosive properties. Therefore, the classification should be applied to GA.

Sensitisation

Skin sensitisation

These chemicals are classified for skin sensitisation which is consistent with classifications for other acrylates and methacrylates. The available data for GMA are also consistent with the current hazard classification. As the induction concentration was changed from 25% to 10% GMA during the Buehler test, it is not possible to recommend a sub-category.

In an in vivo skin sensitisation (Buehler test) study conducted on Hartley guinea pigs, 0.4 mL of a 10–25% GMA solution in dipropylene glycol monomethyl ether (DPGME) was given to the animals in the induction phase. After 2 weeks, the animals were topically challenged with 1% GMA. 7 out of 10 animals showed slight erythema caused by the test substance (ECHA 2015a; OECD 2000; REACH).

Positive results were also observed in non-guideline delayed allergic reaction tests and rapid allergic reaction test (ECHA 2015a).

Several acrylates and methacrylates are classified for skin sensitisation on the HCIS (Safe Work Australia).

Observation in humans

Cases of allergic contact hypersensitivity (N=3) were reported in an adhesive sealant manufacturing unit. Both closed and open patch testing (1% GMA in petrolatum) were reported to have positive results for sensitisation with erythema, oedema, and vesiculation (; ECHA 2015a; OECD 2000; REACH).

A human patch test was conducted on a 31 year old non-atopic woman with frequent contact to acrylate derivatives in relation to her work. In this patch test, she showed skin reactions to GMA at 0.01 % and 0.05 % in acetone (ECHA 2015a; OECD 2000; REACH).

Repeat dose toxicity

Based on the available data for GMA, the main repeat dose toxicity effects of these chemicals are tissue damage at the site of contact. This finding is consistent with the reactivity of these chemicals at the site of contact.

GMA is classified as HCIS (Safe Work Australia) as ‘Specific target organ toxicity repeated exposure (STOT RE)—Category 1’. Local effects in the upper respiratory tract were observed in all repeated dose inhalation studies with GMA. Although these effects are consistent with the corrosive nature of the chemical, effects on the respiratory tract by inhalation occurred at doses significantly lower than those observed following acute exposure. No repeated dose toxicity data are available for GA, but it is expected to cause similar damage to the respiratory tract based on its corrosive properties.

Oral

A combined repeated dose and reproductive/developmental toxicity study (OECD TG 422) was conducted in SD (Crj:CD) rats (n=12/sex/dose) using GMA in corn oil. Dose levels of 10, 30 and 100 mg/kg bw/day were administered by gavage for 45 days in males and from 14 days before mating to day 3 of lactation in females (40–47 days). Salivation was observed in 5/12 males from the 30 mg/kg bw dose group and in 12/12 males from the 100 mg/kg bw

dose group. In the 100 mg/kg bw/day dose group, an increase in absolute and relative kidney and adrenal weights was reported in all treated males. Squamous hyperplasia in the forestomach was observed in mid and high dose group males and cellular infiltration in the forestomach was observed in females in the 100 mg/kg bw dose group at histological examination. These histological changes were considered by the study authors to be due to the severe irritation caused by GMA. The NOAEL for oral repeat toxicity for systemic effects was 30 mg/kg bw/day for males and females (ECHA 2015; OECD 2000; REACH).

Dermal

No data are available for these chemicals.

Inhalation

In an inhalation toxicity study, F344/N rats were exposed to GMA vapours at concentrations of 2.9, 12 or 87 mg/m^3 for 13 weeks (6 hours/day, 5 days/week), which is equivalent to 0.35, 1.46 or 10.6 mg/kg bw/day. There was no treatment related clinical observations, and no significant effects on body weight, urinalysis, clinical chemistry, haematology parameters, gross pathologic changes or organ weights, at any exposure level. Treatment related effects included hyperplasia of respiratory epithelium of the nasal tissues in all animals in the high dose group. The hyperplastic respiratory epithelium was approximately 2 to 3 times as thick as in control animals and was located in the anterior portions of the nasal passages, involving the tips of the turbinates and the lateral walls of the nasal passages. These changes were considered to be due to respiratory irritation caused by the test substance. Therefore, the no observed adverse effect concentration (NOAEC) was considered by the study authors to be at 12 mg/m^3 for both sexes (ECHA 2015; OECD 2000).

A subacute inhalation toxicity study was conducted in F344/N rats (n= 5/sex/dose) using GMA. The animals were exposed to concentrations of 58.2, 233 or 931 mg/m^3 for 2 weeks (6 hours/day, 5 days/week), which is equivalent to 7.09, 28.4 or 113 mg/kg bw/day. Decreases in body weight were observed at the mid and high dose. Animals in the high dose group showed general debilitation with noisy and difficult respiration with mouth breathing, eye irritation, corneal clouding and distended abdomen. The animals in the high dose group were terminated on day 4 due to severe respiratory and ocular effects caused by the test substance. Necropsy results showed severe multifocal necrosis and inflammation of the olfactory epithelium in the nasal cavity in the mid dose group. Animals in the low dose group showed very slight multifocal necrosis of individual respiratory epithelial cells in 3/5 males and 2/5 females. These changes in the respiratory tract were considered to be due to irritation caused by the test substance. No histopathological changes in any other tissues were observed. A LOAEC of 58.2 mg/m^3 was reported based on the observed tissue damages in the respiratory tract (ECHA 2015; OECD 2000; REACH).

In an inhalation toxicity study conducted in NZW rabbits, the animals were exposed to GMA vapours (92 % purity) at 2.91, 11.6, 29.1, 58.2 mg/m^3 (6 or 7 hours/day, daily) for 13 consecutive days. Treatment related degeneration of the nasal olfactory epithelium was observed at 11.6 mg/m^3. Effects observed at 29.1 and 58.2 mg/m^3 included olfactory epithelial degeneration, hyperplasia, erosions, ulcers and inflammation of the nasal epithelium. After a 4 week recovery period effects had completely reversed, except for the olfactory epithelial degeneration observed at 29.1 and 58.2 mg/m^3, which was partially reversed. A NOAEC of 2.91 mg/m^3 was reported (ECHA 2015; OECD 2000)

Genotoxicity

Based on the available data, these chemicals are considered to be genotoxic. The available data for GMA (positive somatic cell mutagenicity test supported by positive in vitro tests and known genotoxicity of the metabolite glycidol) are consistent with the current hazard classification. Given the structural similarity and common metabolite (glycidol), this classification is also warranted for GA.

Several in vitro tests gave positive results for GMA (ECHA 2015; IARC 2020; OECD 2000; REACH):

- Two bacterial reverse mutation tests with *Salmonella typhimurium* (positive in strains TA97, TA100, TA1535 with and without metabolic activation).
- A SOS-chromotest with *Escherichia coli* with and without metabolic activation
- a bacterial gene mutation assay using *S. typhimurium* (positive with strain TA100 with and without metabolic activation).
- A gene mutation analysis with *E. coli* HB101.
- A bacterial gene mutation assay using *Klebsiella pnuemoniae* without metabolic activation.
- An in vitro mammalian chromosomal aberration test in Chinese hamster lung (CHL/IU) cells, with and without metabolic activation.
- A gene mutation tests in Chinese hamster ovary (CHO) cells with metabolic activation.
- An unscheduled DNA synthesis in human and rat lymphocytes.
- A DNA replication assay in human and rat lymphocytes.
- A sister-chromatid exchange assay in Chinese hamster V79 cells without metabolic activation.
- A mammalian cell transformation assays in Syrian hamster embryonic cells (SHE) and in diploid golden SHE cells.
- A DNA binding study in calf thymus DNA.

In a micronucleus assay, BDF1 mice were administered GMA by gavage at single doses of 188, 375 and 750 mg/kg bw in males and 250, 500 and 1000 mg/kg bw in females. The frequency of micronucleated polychromatic erythrocytes in both sexes was significantly increased at the highest doses, 48 hours after administration.

The genotoxicity of GMA was assessed in an in vivo study on F344 rats. The rats were administered the chemical orally at doses of 50, 100 and 150 mg/kg bw/day for 29 days, with another dose group of 250 mg/kg bw/day for 3 days. Clastogenicity was measured by scoring micronucleated (MN) erythrocytes from peripheral blood. The DNA damage in liver, bone marrow and kidneys were measured using the comet assay, and gene mutation was measured using the red blood cell (RBC) and reticulocyte Pig-a assay. Positive results for genotoxicity were observed, including a dose dependent increase of micronucleated reticulocytes, increased frequencies of mutant red blood cells and reticulocytes, and DNA damage in tissues harvested from the bone marrow, liver and kidneys. DNA damage was statistically significant for liver and bone marrow in animals treated for 29 days at the highest 2 doses and for all 3 organs for animals treated for 3 days to the higher dose of 250 mg/kg bw/day. Although treatment related damage was observed in the forestomach, it was not possible to assay cell tissue from this organ for genotoxicity assessment. Based on these results, the authors concluded that GMA was genotoxic and mutagenic in rats after repeated dosing (Dobrovolsky 2016, IARC 2020).

In a non-guideline unscheduled DNA synthesis assay, mice were administered GMA by intraperitoneal (ip) injection at doses of 25, 50 and 100 mg/kg bw. An increase in unscheduled DNA synthesis in germ cells was observed, but this was very slight and not dose related (ECHA 2015a). This study was not considered to provide direct evidence that GMA is bioavailable to germ cells and able to induce mutagenicity in germ cells (ECHA 2015b, IARC 2020).

Other in vivo genotoxicity studies were mostly reported to be negative, including micronucleus tests with ip administration and a gene mutation study with transgenic Big Blue F344 rats. Three mouse micronucleus tests by ip administration were reported. In the one fulfilling OECD criteria CD-1 mice were administered GMA at dose levels of 75, 150 and 300 mg/kg bw/day. There was no statistically significant increase in the frequency of micronucleated polychromatic erythrocytes.

Limited data are available for genotoxicity with GA. In a bacterial mutagenicity test conducted in *S. typhimurium* strains TA97, TA98, TA100 and TA1535, GA gave positive results in strains TA97, TA100 and TA1535, but not TA98 (NTP 2018).

These chemicals are expected to be metabolised to glycidol. The genotoxicity potential of glycidol should also be considered when determining the genotoxic potential of these chemicals. Glycidol has been classified by Safe Work Australia and the former NICNAS for Germ cell mutagenicity – Category 1B (NICNAS 2014a).

Carcinogenicity

GMA is classified as hazardous as a Category 1B carcinogen with the risk phrase 'May cause cancer' in the HCIS (Safe Work Australia). The available data for GMA are consistent with this classification. Given the structural similarity and common metabolite (glycidol), this classification is also warranted for GA.

The IARC 2020 has classified GMA as 'Probably carcinogenic to humans' (Group 2A), based on inadequate evidence for carcinogenicity in humans, but sufficient evidence in experimental animals.

In a 2 year carcinogenicity study, F344/N rats (50/sex/dose) were exposed to GMA (purity >99%) vapours at concentrations of 0, 3.2, 8, or 20 ppm (v/v) for 6 hours/day, 5 days/week for 104 weeks. Survival rates were significantly lower in males and females at 20 ppm as compared to the controls. Body weights in males at 20 ppm was significantly lower throughout the study period, while in females at 20 ppm, they were lower for last half of the study period. Incidence of squamous cell carcinomas of the nasal cavity was significantly increased in high dose males and females. Neuroepithelial carcinoma (esthesioneuroepithelioma) of the nasal cavity, mesothelioma of the peritoneum, subcutis fibroma, adenomas of the nasal cavity, basal cell epithelioma and keratoacanthoma of the skin were observed in male rats, while female rats had endometrial stromal sarcoma of the uterus, fibroadenomas of the mammary gland, subcutis fibroma, thyroid C-cell adenomas and adenoma of the clitoral glands. Non-neoplastic lesions in the nasal cavity, squamous cell hyperplasia with atypia, cell metaplasia in the respiratory epithelium and transitional epithelium hyperplasia were also reported at multiple doses in males and females (IARC 2020).

In a 2 year carcinogenicity study, B6C3F1 mice (50/sex/dose) were exposed by whole body inhalation to GMA (purity >99%) vapours at concentrations of 0, 0.6, 2.5, or 10 ppm (v/v) for 6 hours/day, 5 days/week for 104 weeks. Survival rate in male mice was significantly lower at

2.5 and 10 ppm concentrations. Multiple dose dependent tumours were induced in mice exposed to the chemical. Significant positive trends and increase in the incidences of haemangioma or haemangiosarcoma (combined) of the nasal cavity were reported in males and females. Tumours of the Harderian gland were the most frequently observed in males and females. Male mice also had adenomas of the nasal cavity and squamous cell papillomas of the forestomach, while female mice were reported to have bronchioloalveolar carcinomas and histiocytic sarcomas in the uterus (IARC 2020).

There were no observed increase in the incidence of tumours either in a 1 year gavage study in F344/N rats or 26 week inhalation study in rats and rabbits. A number of limitations were noted in these studies including limited experimental detail and duration (ECHA 2015b, IARC 2020)

These chemicals are expected to be metabolised to glycidol. Glycidol has been classified by Safe Work Australia and the former NICNAS for Carcinogenicity – Category 1B (NICNAS 2014a).The tumour site profile of glycidyl methacrylate is similar to that reported in carcinogenicity bioassays with glycidol (IARC 2020)

Reproductive and development toxicity

GMA is classified as hazardous as a Category 1B substance with risk phrase 'May damage fertility' in HCIS (Safe Work Australia). The available data for GMA are consistent with this classification. Given the structural similarity and common metabolite (glycidol), this classification is also warranted for GA.

A combined repeated dose and reproductive/developmental toxicity screening test (OECD TG 422) was conducted in rats using GMA. Dose levels of 10, 30 and 100 mg/kg bw/day were administered by gavage for 45 days in males and from 14 days before mating to day 3 of lactation in females (40–47 days). The fertility index (number of delivered pups/number of mated animals) decreased significantly at the highest dose. There were no observed changes on the oestrous cycle, copulation index, or gestation length. No significant changes in the numbers of corpora lutea, implants, pups born and live pups, implantation and delivery indices were observed. There were no significant differences in the gestation index, live birth index or viability index on day 4. Histopathological analysis of the gonads showed no significant effects that could be linked to infertility. No changes in the number of gonocyte per Sertoli cell were observed in epithelium of seminiferous tubule (stage VIII) of all surviving males in the high dose group. No sperm analysis was performed in the original investigation as this is not required according to OECD TG 422. Secondary investigations showed reduced motility in sperm but no further details were available. No treatment related abnormalities were noted in the body weights of live pups or during necropsy of pups in any treated group. Therefore, NOAELs for reproductive performance of parents and pup development were considered to be 30 mg/kg bw/day and 100 mg/kg bw/day, respectively (ECHA 2015, OECD 2020, REACH).

In a study investigating impact on sperm parameters, male CD-1 mice (n=5) were injected ip with daily doses of 0, 25, 50 or 100 mg/kg bw/day of GMA for 5 consecutive days. Increases in the percentage of abnormal sperm and decreases in the number of sperm was observed. These results were confirmed in a subsequent study where mice were injected ip with daily doses of 0, 5, 25 or 100 mg/kg bw for 5 consecutive days. Mice in the 100 mg/kg bw/day dose group had decreased caudal epididymal weights, slightly lower testicular weights, decreased sperm counts and increased abnormal sperm. Animals in the 25 mg/kg bw/day

dose group showed decreased sperm counts and increased abnormal sperm. An NOAEL of 5 mg/kg bw/day was reported for sperm toxicity (ECHA 2015, OECD 2020).

In a developmental toxicity study, GMA was administered by gavage to female Wistar rats (n=93) during day 5 to day 15 of gestation at doses of 5.38, 10.8, 21.5 and 108 mg/kg bw/day. All treated animals were sacrificed on day 19 of pregnancy. A statistically significant decrease in body weight gain and increase in foetal resorption rate were observed in females at 108 mg/kg bw/day. The percentage of stillborn pups was slightly higher at all dose levels compared with controls. This was not dose dependent and was only statistically significant in the 10.8 mg/kg bw/day dose group. No birth defects or foetal abnormalities were noted, and no statistically significant foetal weight change was observed. The NOAELs were 21.5 mg/kg bw/day for maternal toxicity and 108 mg/kg bw/day for teratogenicity (ECHA 2015, OECD 2020, REACH).

In a developmental toxicity study conducted in NZW rabbits, the animals were exposed to GMA by inhalation at concentrations of 29.1, 58.2 and 291 mg/m^3, for 6 hours/day, daily (equivalent to 2.62, 5.24 and 26.2 mg/kg bw/day) on day 7 to day 19 of gestation. Respiratory distress and decrease in feed consumption were observed in the highest dose group. Less severe signs of ocular and respiratory irritation consisting of reddened eyes, wet muzzle and sneezing were observed in the mid dose group. Treatment related effects include histopathologic alterations of the nasal tissues, including hyperplasia and necrosis, observed in all animals treated with the chemical. Treatment of animals in the highest dose group was prematurely stopped after the third exposure due to significant respiratory distress. Therefore, evaluation of reproductive and developmental were precluded. There were no adverse effects on any reproductive and developmental parameters at 29.1 and 58.2 mg/m^3. An LOAEL for maternal toxicity was 29.1 mg/m^3 (2.62 mg/kg bw/day) and NOAEL for developmental toxicity was 58.2 mg/m^3 (5.24 mg/kg bw/day) (ECHA 2015, OECD 2020, REACH).

In a developmental toxicity study conducted in NZW rabbits, the animals were exposed to GMA by inhalation at concentrations of 2.91, 11.6 and 58.2 mg/m^3 for 7 hours/day, daily (equivalent to 0.31, 1.22 and 6.11 mg/kg bw/day) on day 7 to day 19 of gestation. Signs of maternal toxicity included inflammation of the nasal olfactory and respiratory epithelium in the mid and high dose groups. There were no developmental effects at any doses. An NOAEL for maternal toxicity was established to be 2.91 mg/m^3 (0.31 mg/kg bw/day) and the NOAEL for developmental toxicity was 58.2 mg/m^3 (6.11 mg/kg bw/day) (ECHA 2015, OECD 2020, REACH).

These chemicals are expected to be metabolised to glycidol. Glycidol has been classified by Safe Work Australia and the former NICNAS ‘May damage fertility – Cat 1B (H360F)’. Studies investigating fertility showed that glycidol induced male infertility (ECHA 2015b; NICNAS 2014a).

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